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Catalyst-free alkylation of aminopyrazole by isatin in water

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Reactions of isatins with 5-aminopyrazole afforded the 3-(5-aminopyrazol-4-yl)-3-hydroxy-2-oxindolines in good to excellent yields in refluxing water. No catalysts were required in the process. The new method exhibited the characteristics including green process, high yields, easy operation, and mild reaction conditions.

alkylation, aminopyrazole, isatin, catalyst-free, water

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Oxindole derivatives have long been the focus of considerable attention due to their abundance in numerous natural products as well as their extensive applications in biology and pharmacology [1–5]. A great number of compounds bearing oxindole moieties are reported to possess significant antibacterial, antiprotozoal, antiinflammatory and antitumor properties [6,7], and they have been widely employed as potential synthons for the synthesis of alkaloids, drug candidates and clinical pharmaceuticals [8–10]. Isatin-based alkylation is one of the most important strategies for the construction of oxindole skeleton, especially for those bearing a hydroxyl substituent at the C-3 position which also possess various bioactivities [11,12]. Compared with Friedel-Crafts alkylation of indole with isatin for access to the monosubstituted 3-indolyl-3-hydroxy oxindoles [13–15], related study on alkylation of aminopyrazole was rare, although pyrazole had also been confirmed to provide privileged scaffolds in lead identification/drug discovery programs as well as therapeutically useful compounds in fields such as cyclooxygenase inhibitors (e.g., SC-558, tepoxalin, and celecoxib) and cannabinoid-1 inverse agonists which are very promising for reducing obesity (e.g., rimonabant) [16]. Since the first report on the alkylation of 5-aminopyrazole with isatin by molecular iodine in organic solvent [17], the same organic transformation has been successfully achieved in water by using indium catalyst [16,18]. In our continuous work focused on organic reactions in water, we found the alkylation of 5-aminopyrazole with isatin could be well performed in pure water without the need of any catalyst. The green protocol provided the products in high to excellent yields. Herein, we report these results.

1 Experimental

1.1 General information

Melting points were uncorrected. Progresses of reactions were monitored by Thin Layer Chromatography (TLC). IR spectra were recorded on an FT-IR spectrometer using KBr optics. NMR spectra were recorded at room temperature in DMSO-d_6 at 300/400 and 75/100 Hz. High resolution mass spectra (HRMS) were obtained on a TOF MS instrument with EI or ESI source.

1.2 General procedure for the synthesis of 3

A mixture of isatin **1** (0.5 mmol), aminopyrazole **2** (0.5 mmol) in 3 mL water was placed in a round bottom flask.

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The reaction was carried out at refluxing for a specific time (the progress was monitored by TLC). After completion of the reaction, the reaction mixture was cooled and filtered. Then the precipitate was washed with 70% ethanol for three times to afford the pure **3**.

1.3 Characterization data

3-(5-amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5-chloro-3-hydroxyindolin-2-one (**3aa**). Light yellow solid; m.p. 220–222°C; IR (KBr): *v* 3401, 3298, 2801, 1706, 1620, 1447 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.51 (s, 1 H, NH), 7.57 (d, *J* = 7.6 Hz, 2 H, ArH), 7.47 (t, *J* = 7.2 Hz, 2 H, ArH), 7.29–7.32 (m, 3 H, ArH), 6.89 (d, *J* = 8.0 Hz, 1 H, ArH), 6.77 (s, 1 H, OH), 5.30 (s, 2 H, NH_2), 1.50 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 177.9, 146.4, 144.4, 140.5, 138.9, 134.9, 129.3, 129.2, 126.2, 126.1, 124.9, 122.9, 111.5, 99.1, 74.6, 12.8; HRMS (EI) calcd. for $C_{18}H_{15}ClN_4O_2$ (M) 354.0884, found 354.0890.

3-(5-amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5-brom *o*-3-hydroxyindolin-2-one (**3ba**). Light yellow solid; m.p. 209–211°C; IR (KBr) : *v* 3498, 3402, 3296, 2795, 1707, 1617, 1552, 1475, 1385 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.54 (s, 1 H, NH), 7.32–7.58 (m, 7 H, ArH), 6.85 (d, *J* = 6.0 Hz, 1 H, ArH), 6.79 (s, 1 H, OH), 5.31 (s, 2 H, NH_2), 151 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 177.8, 148.3, 144.5, 141.2, 137.5, 132.7, 129.2, 126.3, 125.8, 124.7, 123.8, 118.1 112.7, 98.0, 74.2, 12.4; HRMS (EI) calcd. for $C_{18}H_{15}BrN_4O_2$ (M) 398.0378, found 398.0376.

3-(5-amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)-6-brom *o*-3-hydroxyindolin-2-one (**3ca**) [16]. Light yellow solid; m.p. 206–208°C; IR (KBr) : *v* 3418, 3323, 2974, 1735, 1554, 1528, 1478, 1387 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.54 (s, 1 H, NH), 7.56 (d, *J* = 6.8 Hz, 2 H, ArH), 7.47(s, 2 H, ArH), 7.30 (s, 1 H, ArH), 7.23 (s, 1 H, ArH), 7.19 (d, *J* = 6.4 Hz, 1 H, ArH), 7.02 (s, 1 H, ArH), 6.75 (s, 1 H, OH), 5.32 (s, 2 H, NH_2), 1.47 (s, 3 H, CH_3); HRMS(ESI) calcd. for $C_{18}H_{15}BrN_4O_2^+$($M+H^+$) 398.0378, found, 398.0375.

3-(5-amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)-3-hydro xyindolin-2-one (**3da**) [16]. Light yellow solid; m.p. 218–220°C; IR (KBr) : *v* 3439, 3361, 3126, 2831, 1717, 1521, 1473, 1387 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ:10.30 (s, 1 H, NH), 7.54 (d, *J* = 7.2 Hz, 2 H, ArH), 7.43(t, *J* = 7.2 Hz, 2 H, ArH), 7.21–7.26 (m, 3 H, ArH), 6.96 (t, *J* = 7.2 Hz, 1 H, ArH), 6.83 (d, *J* = 7.6 Hz, 1 H, ArH), 6.57 (s, 1 H, OH), 5.24 (s, 2 H, NH_2), 1.43 (s, 3 H, CH_3); HRMS (EI) calcd. for $C_{18}H_{16}N_4O_2$ (M) 320.1273, found 320.1273.

3-(5-amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)-4-chlor *o*-3-hydroxyindolin-2-one (**3ea**). Light yellow solid; m.p. 228–230°C; IR (KBr) : *v* 3442, 3324, 3028, 1721, 1566, 1524, 1382 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.53 (s, 1 H, NH), 7.48 (d, *J* = 7.6 Hz, 2 H, ArH), 7.36 (t, *J* = 7.2 Hz, 2 H, ArH), 7.15–7.18 (m, 2 H, ArH), 6.87 (d, *J* = 8.0 Hz, 1 H, ArH), 6.73 (d, *J* = 7.6 Hz, 1 H, ArH), 6.63 (s, 1 H, OH), 5.22 (s, 2 H, NH_2), 1.35 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 177.5, 147.0, 144.1, 143.8, 139.1, 131.2, 129.1, 128.8, 126.0, 122.7, 122.0, 108.7, 97.3, 75.2, 12.3; HRMS (EI) calcd. for $C_{18}H_{15}ClN_4O_2$ (M) 354.0884, found 354.0884.

3-(5-amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)-3-hydroxy-5-methylindolin-2-one (**3fa**). Light yellow solid; m.p. 218–220°C; IR (KBr) : *v* 3489, 3400, 3298, 3051, 2802, 1703, 1609, 1527, 1492, 1382 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.2 (s, 1 H, NH), 7.47 (d, *J* = 6.8 Hz, 2 H, ArH), 7.35 (d, *J* = 6.4 Hz, 2 H, ArH), 7.17–7.20 (m, 1 H, ArH), 7.0 (s, 1 H, ArH), 6.95 (t, *J* = 3.2 Hz, 1 H, ArH), 6.64 (d, *J* = 7.2 Hz, 1 H, ArH), 6.50 (s, 1 H, OH), 5.20 (s, 2 H, NH_2), 2.14 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 178.3, 146.2, 144.8, 139.2, 139.1, 133.0, 131.0, 129.7, 129.2, 126.1, 125.6, 122.8, 109.6, 99.9, 74.8, 20.8, 12.8; HRMS (EI) calcd. for $C_{19}H_{18}N_4O_2$ (M) 334.1430, found 334.1436.

3-(5-amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5-fluor *o*-3-hydroxyindolin-2-one (**3ga**). Light yellow solid; m.p. 212–214°C; IR (KBr) : *v* 3392, 3310, 2937, 2877, 1713, 1598, 1486, 1385 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.44 (s, 1 H, NH), 7.58 (d, *J* = 7.6 Hz, 2 H, ArH), 7.48 (t, *J* = 7.6 Hz, 2 H, ArH), 7.31 (t, *J* = 7.2 Hz, 1 H, ArH), 7.09–7.16 (m, 2 H, ArH), 6.86–6.89 (m, 1 H, ArH), 6.81 (s, 1 H, OH), 5.34 (s, 2 H, NH_2), 1.49 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 178.3, 159.9, 156.8, 146.4, 144.5, 139.0, 137.9, 134.7, 134.6, 129.2, 126.3, 122.9, 116.0, 115.7, 112.8, 112.4, 110.9, 110.8, 99.3, 74.9, 12.8; HRMS (EI) calcd. for $C_{18}H_{15}FN_4O_2$ (M) 338.1179, found 338.1178.

3-(5-amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)-3-hydroxy-5-methoxyindolin-2-one (**3ha**). Yellow solid; m.p. 245.5–247.8 °C; IR (KBr): *v* 3444, 3344, 3166, 2844, 1720, 1608, 1491, 1378 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.20 (s, 1H, NH), 7.58 (d, *J* = 7.6 Hz, 2H, ArH), 7.47 (t, *J* = 7.2 Hz, 2H, ArH), 7.30 (t, *J* = 7.2 Hz, 1H, ArH), 6.91 (s, 1H, ArH), 6.84 (d, *J* = 8.4 Hz, 1H, ArH), 6.79 (d, *J* = 8.2 Hz, 1H, ArH), 6.63 (s, 1H, OH), 5.29 (s, 2H, NH_2), 3.70 (s, 3H, CH_3), 1.49 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 183.5, 160.5, 151.6, 150.1, 144.4, 140.2, 139.4, 134.5, 131.4, 128.1, 119.7, 116.9, 115.7, 105.1, 80.3, 60.9, 18.2; HRMS (EI) calcd. for $C_{19}H_{18}N_4O_3$ (M) 350.1379, found 350.1374.

3-(5-amino-1,3-dimethyl-1H-pyrazol-4-yl)-5-chloro-3-hydroxyindolin-2-one (**3ab**). Light yellow solid; m.p. 188–190°C; IR (KBr) : *v* 3480, 3375, 3310, 1738, 1608, 1533, 1475, 1378 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.42 (s, 1 H, NH), 7.27 (d, *J* = 8.0 Hz, 1 H, ArH), 7.19 (s, 1H, ArH), 6.84 (d, *J* = 8.0 Hz, 1 H, ArH), 6.56 (s, 1 H, OH), 5.09 (s, 2 H, NH_2), 3.40 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 178.1, 146.3, 141.4, 140.4, 135.3, 129.1, 125.9, 124.8, 111.3, 97.8, 33.7, 12.7; HRMS (EI) calcd. for $C_{13}H_{13}ClN_4O_2$ (M) 292.0727, found 292.0725.

3-(5-amino-1,3-dimethyl-1H-pyrazol-4-yl)-6-bromo-3-

hydroxyindolin-2-one (**3cb**). Light yellow solid; m.p. 202–204°C; IR (KBr) : *v* 3405, 3278, 1715, 1609, 1534, 1448 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.42 (s, 1 H, NH), 7.14 (s, 2 H, ArH), 6.98 (s, 1 H, ArH), 6.50 (s, 1 H, OH), 5.09 (s, 2 H, NH_2), 3.41 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 178.3, 146.4, 143.3, 141.6, 132.6, 126.8, 124.6, 121.8, 112.6, 97.7, 74.3, 33.7, 12.7; HRMS (EI) calcd. for $C_{13}H_{13}BrN_4O_2$ (M) 336.0222, found 336.0224.

3-(5-amino-1,3-dimethyl-1H-pyrazol-4-yl)-5-bromo-3-hydroxyindolin-2-one (**3bb**). Light yellow solid; m.p. 198–200°C; IR (KBr) : *v* 3484, 3388, 3320, 3005, 1734, 1616, 1540, 1474, 1389 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.46 (s, 1 H, NH), 7.30–7.41 (m, 2 H, ArH), 6.80-6.81 (m 1 H, ArH), 6.57 (s, 1 H, OH), 5.1 (s, 2 H, NH_2), 3.42 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 178.0, 146.3, 141.8, 140.8, 135.7, 131.9, 127.5, 113.5, 111.8, 97.8, 74.6, 33.7, 12.7; HRMS (EI) calcd. for $C_{13}H_{13}BrN_4O_2$ (M) 336.0222, found 336.0223.

3-(5-amino-1,3-dimethyl-1H-pyrazol-4-yl)-3-hydroxyindolin-2-one (**3db**). Light yellow solid; m.p. 194–196 °C; IR (KBr) : *v* 3445, 3362, 2817, 1715, 1620, 1539, 1471, 1393 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.25 (s, 1 H, NH), 7.19 (d, *J* = 7.2 Hz, 2 H, ArH), 6.94 (t, *J* = 6.4 Hz, 1 H, ArH), 6.81 (t, *J* = 7.2 Hz, 1 H, ArH), 6.39 (s, 1 H, OH), 5.05 (s, 2 H, NH_2), 3.40 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 178.5, 146.2, 141.7, 133.2, 129.3, 125.0, 121.8, 109.7, 98.3, 74.6, 33.7, 12.6; HRMS (EI) calcd. for $C_{13}H_{14}N_4O_2$ (M) 258.1117, found 258.1120.

3-(5-amino-1,3-dimethyl-1H-pyrazol-4-yl)-4-chloro-3-hydroxyindolin-2-one (**3eb**). Light yellow solid; m.p. 197–199°C; IR (KBr) : *v* 3454, 3336, 3020, 1724, 1618, 1557, 1464, 1378 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.49 (s, 1H, NH), 7.23 (t, *J* = 7.6 Hz, 1H, ArH), 6.93 (d, *J* = 8.0 Hz, 1H, ArH), 6.80 (d, *J* = 7.5 Hz, 1H, ArH), 6.47 (s, 1H, OH), 5.06 (s, 2H, NH_2), 3.41 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 183.1, 152.2, 149.1, 146.4, 136.5, 136.3, 134.3, 127.9, 113.9, 101.2, 80.6, 39.0, 17.4; HRMS (EI) calcd. for $C_{13}H_{13}ClN_4O_2$ (M) 292.0727, found 292.0719.

3-(5-amino-1,3-dimethyl-1H-pyrazol-4-yl)-3-hydroxy-5-methylindolin-2-one (**3fb**). Light yellow solid; m.p. 160–162°C; IR (KBr) : *v* 3375, 3314, 3019, 2810, 1735, 1613, 1476, 1450, 1388 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.50 (s, 1 H, NH), 7.23 (t, *J* = 7.6 Hz, 1 H, ArH), 6.93 (d, *J* = 8.0 Hz, 1 H, ArH), 6.79 (d, *J* = 7.6 Hz, 1 H, ArH), 6.49 (s, 1 H, OH), 5.06 (s, 2 H, NH_2), 3.41 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 177.7, 146.7, 143.6, 141.1, 131.8, 128.9, 122.4, 108.4, 95.9, 75.1, 33.6, 21.2, 12.0; HRMS (EI) calcd. for $C_{14}H_{16}N_4O_2$ (M) 272.1273, found 272.1270.

3-(5-amino-1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoro-3-hydroxyindolin-2-one (**3gb**). Light yellow solid; m.p. 193–195°C; IR (KBr): *v* 3447, 3340, 3011, 2858, 1713, 1613, 1550, 1489, 1396 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.32 (s, 1 H, NH), 7.03–7.08 (m, 2 H, ArH), 6.81–6.84 (m, 1 H, ArH), 6.56 (s, 1 H, OH), 5.10 (s, 2 H, NH_2), 3.42 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 183.8, 151.6, 146.8, 143.0, 140.1, 120.8, 117.7, 115.9, 103.3, 80.1, 39.0, 18.0; HRMS (EI) calcd. for $C_{13}H_{13}FN_4O_2$ (M) 276.1023, found 276.1028.

3-(5-amino-3-methyl-1H-pyrazol-4-yl)-5-chloro-3-hydroxyindolin-2-one (**3ac**). Light yellow solid; m.p. 204–206°C; IR (KBr) : *v* 3424, 3345, 3297, 2934, 2849, 1707, 1616, 1473 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 11.22 (s, 1 H, NH), 10.47 (s, 1 H, NH), 7.35 (s, 1 H, ArH), 7.26 (d, *J* = 8.0 Hz, 1 H, ArH), 6.84 (t, *J* = 8.4 Hz, 1 H, ArH), 6.52 (s, 1 H, OH), 4.47 (s, 2 H, NH_2), 1.66s (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 183.3, 145.4, 140.9, 134.7, 134.2, 131.2, 130.0, 116.7, 79.6, 78.6, 16.2; HRMS (EI) calcd. for $C_{12}H_{11}ClN_4O_2$ (M) 278.0571, found 278.0570.

3-(5-amino-3-methyl-1H-pyrazol-4-yl)-5-bromo-3-hydroxyindolin-2-one (**3bc**). Light yellow solid; m.p. 220–222°C; IR (KBr) : *v* 3360, 3277, 3072, 2832, 1712, 1615, 1475 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 11.22 (s, 1 H, NH), 10.49 (s, 1 H, NH), 7.44 (s, 1 H, ArH), 7.39 (d, *J* = 8.0 Hz, 1 H, ArH), 7.80 (t, *J* = 8.0 Hz, 1 H, ArH), 6.53 (s, 1 H, OH), 4.55 (s, 2 H, NH_2), 1.63 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 177.8, 146.0, 141.2, 140.5, 135.9, 131.8, 127.8, 113.5, 111.9, 74.2, 10.9; HRMS (EI) calcd. for $C_{12}H_{11}BrN_4O_2$ (M) 322.0065, found 322.0065.

3-(5-amino-3-methyl-1H-pyrazol-4-yl)-4-chloro-3-hydroxyindolin-2-one (**3ec**). Light yellow solid; m.p. 213–215°C; IR (KBr) : *v* 3424, 3345, 3297, 2934, 2849, 1707, 1616, 1473 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 11.22 (s, 1 H, NH), 10.50 (s, 1 H, NH), 7.25 (t, *J* = 8.0 Hz, 1 H, ArH), 6.95 (d, *J* = 8.0 Hz, 1 H, ArH), 6.81 (d, *J* = 8.0 Hz, 1 H, ArH), 6.38 (s, 1 H, OH), 4.50 (s, 2 H, NH_2), 1.52 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 177.8, 143.6, 131.1, 130.9, 128.9, 108.6, 98.0, 75.1, 10.6; HRMS (EI) calcd. for $C_{12}H_{11}ClN_4O_2$ (M) 278.0571, found 278.0578.

3-(5-amino-3-methyl-1H-pyrazol-4-yl)-3-hydroxy-5-methylindolin-2-one (**3fc**). Light yellow solid; m.p. 236–238°C; IR (KBr) : *v* 3432, 3348, 2828, 1707, 1608, 1536, 1492 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 11.16 (s, 1 H, NH), 10.19 (s, 1 H, NH), 7.11 (s, 1 H, ArH), 7.01 (d, *J* = 8.0 Hz, 1 H, ArH), 6.72 (d, *J* = 8.0 Hz, 1 H, ArH), 6.27 (s, 1 H, OH), 4.45 (s, 2 H, NH_2), 2.23 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 178.5, 138.9, 133.5, 130.7, 129.3, 125.4, 109.5, 74.4, 20.8, 12.3; HRMS (EI) calcd. for $C_{13}H_{14}N_4O_2$ (M) 258.1117, found 258.1118.

3-(5-amino-3-methyl-1H-pyrazol-4-yl)-5-fluoro-3-hydroxyindolin-2-one (**3gc**). Light yellow solid; m.p. 200–202°C; IR (KBr) : *v* 3419, 3339, 3291, 2928, 2845, 1703, 1614, 1470 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 11.12 (s, 1 H, NH), 10.32 (s, 1 H, NH), 7.03–7.08 (m, 2 H, ArH), 6.82 (dd, *J* = 4.0 Hz, 4.0 Hz, 1 H, ArH), 6.56 (s, 1 H, OH), 5.10 (s, 2 H, NH_2), 1.37 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 178.5, 159.8, 156.7, 146.3, 141.5, 137.8, 135.1, 135.0, 115.7, 112.6, 110.7, 97.9, 74.8, 12.6; HRMS (EI) calcd. for

$C_{12}H_{11}FN_4O_2$ (M) 262.0866, found 262.0865.

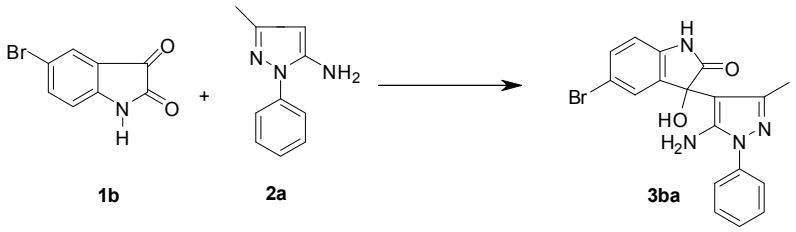
2 Results and discussion

Our initial attempt was focused on the feasibility of the model reaction of isatin **1b** with 5-aminopyrazole **2a** under catalyst-free condition (Scheme 1). It was fortunately found that the reaction could be performed well in acetic acid at 100°C to give the desired product in 80% yield (entry 1, Table 1). A comparable yield was obtained when the reaction was carried out in ethyl acetate (entry 2, Table 1). To our surprise, an improved yield of 91% was afforded when the reaction was performed in refluxing water (entry 3, Table 1). Employment of ethanol as solvent exhibited predicTable decrease of product yield, and the combination of water and ethanol was also successful to produce the satisfactory result (entries 4–5, Table 1). In view of the fact that water was a greener solvent than others and the reaction time was shortest with the use of water as solvent, so the optimal reaction conditions were defined as catalyst-free and refluxing water.

With the success of above optimization, next the substrate scope was examined (Scheme 2). As is seen from Table 2, isatins bearing substituents such as 5-Cl, 5-Br, 6-Br, 4-Cl, 5-Me, 5-F, 5-OMe could work well in the reactions with **2a** to produce the desired products in 88%–95% yield (entries 1–3, 5–8, Table 2). The generality of substrate **2** was also surveyed. Under the established conditions, introduction of **2b** into the reaction system led to a viscous and messy mixture and no isolable product could be obtained, which may be due to the lower melting point of **2b**. Interestingly, when the reaction temperature was decreased to 60 °C, we were gratifying to find that all the reactions proceeded smoothly, giving rise to the final products in good to excellent yields after prolonged reaction times (entries 9–15, Table 2). In addition, 5-amino-3-methylpyrazole **2c** was also proven to be a suitable candidate for the transformation (entries 16–20, Table 2), showing comparable performance when the reaction was manipulated under the same conditions employed for the substrate **2b**.

3 Conclusions

In summary, we have demonstrated a green and efficient approach for the alkylation of aminopyrazole in water under solvent-free conditions. The reactions proceeded effectively

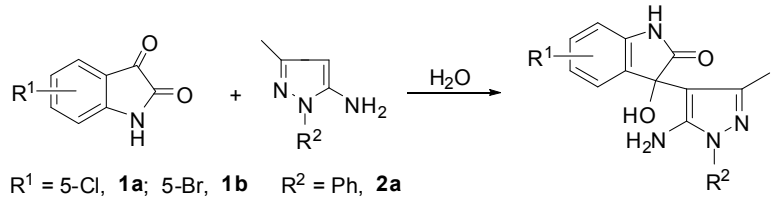


Scheme 1

Table 1 Optimization of reaction conditions [a)]

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)[b)]
1	AcOH	100	12	80
2	EtOAc	80	12	83
3	H_2O	100	4	91
4	EtOH	80	12	85
5	H_2O/EtOH (6:1 v/v)	80	12	90

a) Conditions: **1b** (0.5 mmol), **2a** (0.5 mmol), and solvent (3 mL); b) isolated yield.

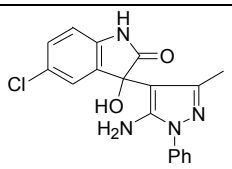
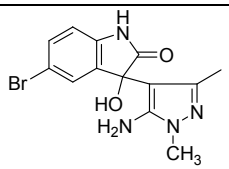
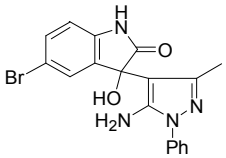
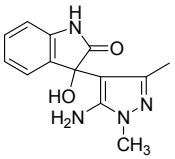
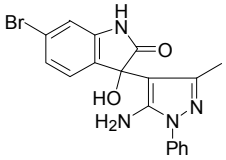
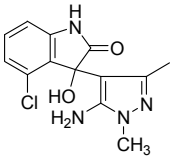
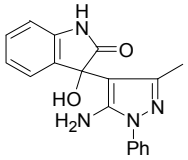
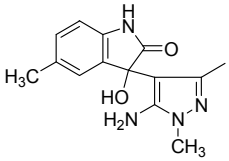
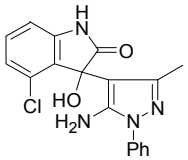
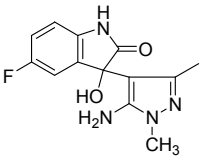
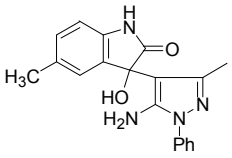
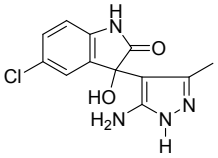
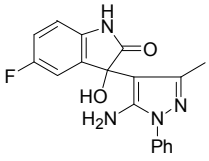
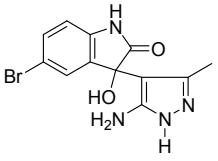
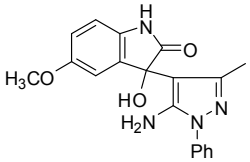
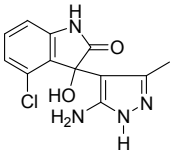
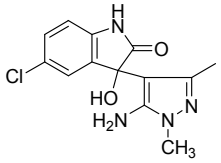
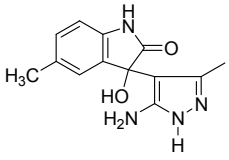
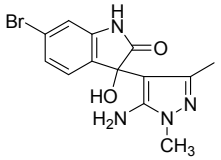
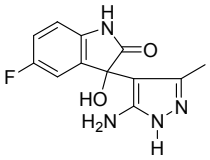


R^1 = 5-Cl, **1a**; 5-Br, **1b**; 6-Br, **1c**; H, **1d**; 4-Cl, **1e**; 5-Me, **1f**; 5-F, **1g**; 5-OMe, **1h**

R^2 = Ph, **2a**; Me, **2b**; H, **2c**

Scheme 2

Table 2 Substrate scope study [a)]

Entry	Product		Time (h)	Yield (%)[b)]	Entry	Product		Time (h)	Yield (%)[b)]
1		**3aa**	5	90	11		**3bb**	15	90
2		**3ba**	4	91	12		**3db**	20	95
3		**3ca**	2	90	13		**3eb**	10	92
4		**3da**	2	95	14		**3fb**	10	93
5		**3ea**	3	92	15		**3gb**	10	95
6		**3fa**	3	88	16		**3ac**	18	85
7		**3ga**	3	90	17		**3bc**	15	80
8		**3ha**	6	90	18		**3ec**	18	90
9		**3ab**	14	86	19		**3fc**	15	88
10		**3cb**	18	88	20		**3gc**	18	90

a) Conditions: **1** (0.5 mmol), **2** (0.5 mmol), and H_2O (3 mL) under refluxing; b) isolated yield.

under optimized conditions to furnish the corresponding products bearing both oxindole and pyrazole moieties in good to excellent yields. The mild reaction conditions, simple manipulation, and the green feature of process make the present method attractive for organic synthesis. In addition, in view of the presence of multi-functionality in the obtained products, these compounds were potentially useful as promising intermediates for many organic transformations.

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1 Da-Silva J F M, Garden S J, Pinto A C. The chemistry of isatins: A review from 1975 to 1999. J Braz Chem Soc, 2001, 12: 273–324
2 Molyneux R J, Elbein A D. The chemistry and biochemistry of simple indolizidine and related polyhydroxy alkaloids. In: Pelletier S W, ed. Alkaloids: Chemical and Biological Perspective. New York: Wiley, 1987. Chapter 1
3 Fujimora S. A class of spiro-oxindoles has been reported as aldose reductase inhibitors. Jap Patent. 1990, Appl 88-2912
4 Galliford C V, Scheidt K A. Pyrrolidinyl-spirooxindole natural products as inspirations for the development of potential therapeutic agents. Angew Chem Int Ed, 2007, 46: 8748–8758
5 Shanmugam P, Viswambharan B, Selvakumar K, et al. A facile and efficient synthesis of highly functionalised 3,3′-dispiropyrrolidine- and 3,3′-dispiropyrrolizidine bisoxindoles via [3+2] cycloaddition. Tetrahedron Lett, 2008, 49: 2611–2615
6 Pajouhesh H, Parsons R, Popp F D. Potential anticonvulsant. VI: Condensation of isatins with cyclohexanone and other cyclic ketones. J Pharm Sci, 1983, 72: 318–321
7 Miyamoto H, Okawa Y, Nakazaki A, et al. Highly diastereoselective one-pot synthesis of spirocyclic oxindoles through intramolecular Ullmann coupling and Claisen rearrangement. Angew Chem Int Ed, 2006, 45: 2274–2277
8 Marti C, Carreira E M. Recent applications to the synthesis of oxindole alkaloids. Eur J Org Chem, 2003, 2209–2219
9 Toyota M, Ihara M. Recent progress in the chemistry of non-monoterpenoid indole alkaloids. Nat Prod Rep, 1998, 15: 327–340
10 Dounary A B, Hatanaka K, Kodanko J J, et al. Enantioselective synthesis of 3-alkyl-3-aryl-oxindoles by catalytic asymmetric intramolecular Heck reactions. J Am Chem Soc, 2003, 125: 6261–6271
11 Frechard A, Fabre N, Pean C, et al. Corrigendum to "Novel indole-type glucosinolates from woad (Isatis tinctoria L.)". Tetrahedron Lett, 2001, 42: 9015–9017
12 Tang Y Q, Sattler I, Thiericke R, et al. Maremycins C and D, new diketopiperazines, and maremycins E and F, novel polycyclic spiroindole metabolites isolated from streptomyces sp. Eur J Org Chem, 2001, 261–267
13 Chauhan P, Chimni S S. Asymmetric addition of indoles to isatins catalyzed by bifunctional modified cinchona alkaloid catalysts. Chem Eur J, 2010, 16: 7709–7713
14 Kumar V P, Reddy V P, Sridhar R, et al. Supramolecular synthesis of 3-indolyl-3-hydroxy oxindoles under neutral conditions in water. J Org Chem, 2008, 73: 1646–1648
15 Rad-Moghadam K, Sharifi-Kiasaraie M, Taheri-Amlashi H. Synthesis of symmetrical and unsymmetrical 3,3′-di(indolyl)indolin-2-ones under controlled catalysis of ionic liquids. Tetrahedron, 2010, 66: 2316–2321
16 Balamurugan K, Perumal S, Menéndez J C. New four-component reactions in water: A convergent approach to the metal-free synthsis of spiro[indoline/acenaphthylene-3,4′-pyrazolo[3,4-*b*]pyridine] derivatives. Tetrahedron, 2011, 67: 3201–3208
17 Pushechnikov A O, Volochnyuk D M, Tolmachev A A. Interaction of izatins with some five-membered aminoheterocycles. Synlett, 2002, 1140–1142
18 Chen H, Shi D Q. Efficient one-pot synthesis of novel spirooxindole derivatives via three-component reaction in aqueous medium. J Comb Chem, 2010, 12: 571–576